



PERIPHERAL ULTRAFILTRATION FOR THE MANAGEMENT OF

ACUTE DECOMPENSATED HEART FAILURE

A Technology Assessment

INTRODUCTION

The California Technology Assessment Forum has been asked to review the scientific literature on the safety and efficacy of peripheral ultrafiltration for the management of patients hospitalized with acute decompensated heart failure.

BACKGROUND

Congestive heart failure (CHF)

Heart failure (HF) is a major public health problem in the United States. Over five million patients in this country have HF, and nearly 500,000 patients are diagnosed with HF for the first time each year. The disorder is the underlying reason for 12 to 15 million office visits and 6.5 million hospital days each year.¹ During the last ten years, the annual number of hospitalizations has increased from approximately 550,000 to nearly 900,000 for HF as a primary diagnosis, and from 1.7 to 2.6 million for HF as a primary or secondary diagnosis.² The primary cause for the hospitalizations is volume overload. Hospitalization for heart failure is a poor prognostic indicator with a two to three month mortality rate of almost nine percent and a rehospitalization rate of about 36%.³

The approach that is most commonly used to quantify the degree of functional limitation imposed by HF is one first developed by the New York Heart Association (NYHA).⁴ This system assigns patients to one of four functional classes, depending on the degree of effort needed to elicit symptoms: patients may have symptoms of HF at rest (class IV), on less-than-ordinary exertion (class III), on ordinary exertion (class II), or only at levels of exertion that would limit normal individuals (class I).

Patients admitted with heart failure generally are volume overloaded. The primary approach to treatment of such episodes is intravenous (IV) diuretic therapy, usually with IV furosemide, to relieve symptoms and improve oxygenation.⁵ Additionally, patients commonly receive a vasodilator such as nitroglycerin, morphine and respiratory support with supplemental oxygen or mechanical ventilation. Patients who do not respond to

initial therapy may require higher doses of loop diuretics, the addition of a thiazide diuretic. If cardiac output is low, the patient may benefit from the addition of inotropic support with dopamine, dobutamine or milrinone.⁵ Nesiritide may also be helpful in selected cases, but there are concerns that nesiritide can increase the risk of renal failure and death compared to other forms of IV vasodilator therapy.^{6,7}

Ultrafiltration

Ultrafiltration has a long history in heart failure. The first paper describing the use of ultrafiltration to treat volume overload in patients with renal failure appeared in the *New England Journal of Medicine* in 1974.⁸ The first use of ultrafiltration to treat volume overload in patients with heart failure was described in 1978.⁹ The early trials required specialized hospital units and both equipment and either arteriovenous or central venovenous vascular access similar to that used for hemodialysis. It was not until 2003 that investigators published case series describing an ultrafiltration device designed for use with peripheral venous access.¹⁰

Patients admitted with acute decompensated heart failure who have been on high dose diuretics as an outpatient often have an inadequate response to IV diuretic therapy.¹¹ IV diuretics may also have significant adverse side effects including severe electrolyte abnormalities, renal dysfunction, and neuroendocrine activation.¹¹⁻¹⁴ The hormone system activated by diuretics includes increases in renin, angiotensin II, aldosterone, norepinephrine, and vasopressin.^{13, 15-18} Ultrafiltration offers another method to remove water and sodium at an adjustable rate without affecting serum electrolytes. Ultrafiltration differs from dialysis because it works by convection rather than diffusion, which reduces the risk for induced metabolic abnormalities.¹⁹ Conventional ultrafiltration devices required central venous access with a double lumen catheter, monitoring by a dialysis technician, and specialized hospital units. More recently, devices have been developed that allow ultrafiltration to be performed through large peripheral venous catheters.

At least eight case series describing the use of ultrafiltration with central venous access in 169 patients have been published.²⁰⁻²⁸ The majority describe the effects of ultrafiltration on patients with class IV heart failure refractory to medical management. The studies consistently reported that ultrafiltration successfully removed volume and relieved symptoms without causing hemodynamic instability or renal dysfunction. In most, fluid was removed at rates up to 500 ml per hour which was continued until right atrial pressure decreased by 50%.

Two small randomized clinical trials using central venous access that were done in Italy suggested that ultrafiltration may offer important benefits compared with diuretic therapy. The first study randomized 24 patients with clinically stable heart failure and an ejection fraction less than 35% to either one treatment with ultrafiltration or usual care.²⁹ An average of 1.9 liters of fluid was removed during ultrafiltration. Treated

patients had a reduction in pulmonary congestion on chest radiographs and reductions in both right and left sided filling pressures in the heart. More importantly, treated patients had greater improvements in both peak exercise capacity ($p < 0.02$) and total exercise tolerance time ($p < 0.02$) compared with controls and the differences were preserved through 90 days of follow-up. However, the ejection fraction did not significantly change with ultrafiltration.

The second study randomized 16 patients with clinically stable heart failure for at least six months who were all being treated with an ACE inhibitor, digoxin, and oral furosemide. The patients were randomized to ultrafiltration or supplementary furosemide with matching on age, sex, and peak exercise capacity. The ultrafiltration group received one treatment that was stopped once right atrial pressures decreased by 50%. The mean volume removed was 1.7 liters (range 1.2 to 2.6 liters). The diuretic group received an IV bolus of 160 mg of furosemide followed by a continuous infusion at 1 mg/min that was stopped once right atrial pressures decreased by 50%. Initially, the average plasma renin level increased less in the ultrafiltration group (+40% versus +170%), but plasma norepinephrine increased more (+80% versus +40%). Over the next four days, the values of plasma norepinephrine, renin, and aldosterone in the ultrafiltration group became increasingly lower than those in the diuretic group ($p < 0.01$ at day four and three months after the intervention). Similarly differences in body weight, congestion scores on chest radiographs, peak exercise tolerance and exercise tolerance time all significantly favored ultrafiltration by day four and remained significant at three months ($p < 0.01$ for all four measures). The underlying mechanism for these improvements with ultrafiltration compared with diuretic therapy were not clear from this study, nor are they fully understood today.

Peripheral ultrafiltration

The peripheral devices recently developed for ultrafiltration usually have three components: catheters for venous access, a disposable filter circuit, and a console unit. The console allows the provider to specify the rate and amount of fluid removed, usually up to 500 cc per hour for up to eight hours. The filter allows fluid to pass through, but maintains electrolyte levels in the normal range. The goal is to remove fluid without significantly affecting electrolyte levels, blood pressure, or heart rate. The procedure requires anticoagulation, usually with heparin, to prevent clotting of the filter. A pressure gradient drives water across a semi-permeable membrane and solutes follow by osmosis at concentrations equivalent to those in plasma. The amount of sodium removed is thus close to 140 mEq per liter and the amount of potassium lost is only about 4 mEq per liter. This compares to approximately 90 mEq of sodium per liter in the urine of salt-restricted, diuretic treated patients and 30 mEq per liter of potassium.³⁰ Thus, ultrafiltration removes sodium more efficiently without removing significant amounts of potassium.

Technology Assessment (TA)

TA Criterion 1: The technology must have the appropriate regulatory approval.

In April 2004, the Aquadex System 100 fluid removal system (CHF Solutions, Brooklyn Park, MN) received FDA 510(k) clearance as substantially equivalent to the System 100 (approved in January 2002). On February 2, 2006 the Aquadex FlexFlow™ System received FDA 510(k) marketing clearance. The Aquadex FlexFlow System is indicated for:

- Temporary (up to 8 hours) ultrafiltration treatment of patients with fluid overload who have failed diuretic therapy; and
- Extended (longer than 8 hours) ultrafiltration treatment of patients with fluid overload who have failed diuretic therapy and require hospitalization.

All treatments must be administered by a health care provider, under physician prescription, both of whom having received training in extracorporeal therapies.

TA Criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The Medline database, Cochrane clinical trials database, Cochrane reviews database and the Database of Abstracts of Reviews of Effects (DARE) were searched using the key words ultrafiltration and hemofiltration. These were cross-referenced with the keywords congestive heart failure and human. The search was performed for the period from 1966 through May 2007. The bibliographies of systematic reviews and key articles were manually searched for additional references and references were requested from the device manufacturers. We also reviewed “related articles” in PubMed for each of the key clinical trials. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full.

The search identified two randomized trials^{31, 32} and three small case series.^{10, 33, 34} Only one of the randomized trials, the recently published Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure (UNLOAD) trial³¹, was large enough to evaluate patient-

oriented health outcomes. It is important to note that the trials do not directly assess the FDA approved indication for peripheral ultrafiltration: patients with volume overload who have failed IV diuretic therapy. Instead, most of these studies evaluated all patients being admitted to the hospital with heart failure, regardless of their response to diuretics.

Level of evidence: 1, 2 and 5

TA Criterion 2 is met.

TA Criterion 3: The technology must improve the net health outcomes.

Heart failure is defined primarily by patients' symptoms. Thus, measurements of symptoms, exercise tolerance and quality of life are important outcomes to assess. Overall symptoms are usually measured from the patient's perspective using the NYHA classification described above.⁴ Many objective measures of exercise tolerance are used, but the most common is the distance in meters walked during six minutes.³⁵ Finally, the standard measure of quality of life for patients with heart failure is the Minnesota Living with Heart Failure Questionnaire (MLHFQ).³⁶ The MLHFQ is a validated measure of the patients' perceptions of the effects of congestive heart failure on their lives. It is a 21 item, self-administered questionnaire that covers physical, socioeconomic and psychological impairments that patients often relate to their heart failure. A score based on how each person ranks each item on a common scale is used to quantify the extent of impairment and how it is affected by therapeutic intervention. The score ranges from 0 to 105 with higher scores indicating more severe symptoms and lower quality of life.

The most important health outcome of HF treatment is survival. Clinical trials large enough to demonstrate an important reduction in overall mortality are feasible because the one-year mortality in patients with Class III and IV HF is over 30%. It is important to note that most of the primary outpatient therapies used to treat HF (beta-blockers, ACE inhibitors, and spironolactone) have individually been shown in randomized clinical trials to reduce total mortality.^{37, 38}

Hospitalization rates for patients with class III and IV HF are also very high.³⁹ Thus, the rate of hospitalization or rehospitalization is an important secondary outcome that should also be considered when evaluating the risks and benefits of therapies for HF. This is particularly relevant for inpatient therapies like peripheral ultrafiltration. In recent studies of optimally treated patients, more than one third of patients hospitalized with heart failure were rehospitalized within three months.³ Thus, the most important health

outcomes to consider in assessing inpatient therapies for heart failure should include hospital length of stay, 30 day mortality, and three month rehospitalization rates.

Case Series

The primary value of case series is initially to provide accurate estimates for rates of adverse events, long term harms and to identify subgroups that may benefit to a greater or lesser extent from the device. These aims require prospective, systematic collection of outcomes data, including adverse events, with nearly complete follow-up.

Three case series of peripheral ultrafiltration in a total of 50 patients have been published. In the first study, 21 patients with volume overload primarily from CHF received a total of 25 ultrafiltration treatments with the Simple Access Fluid Extraction (SAFE) UFC 100 console (CHF Solutions, Minneapolis, MN). Treatment was successful (at least 1 liter of fluid was removed) in 92% (23/25) of the attempts. The average volume removed was 2.6 liters. There were no significant changes in heart rate, blood pressure, creatinine, or hematocrit levels in the 24 hours following treatment. No serious adverse events were reported. Minor adverse events included three patients with vomiting, one with erythema at the IV site, one urinary tract infection, and one case of transient hypoxemia. This was the first report of ultrafiltration being performed without central venous access. It demonstrated the feasibility and safety of the procedure, but did not report any patient-oriented outcomes and only followed patients for the first 24 hours after treatment.

The second case series³⁴ evaluated the use of peripheral ultrafiltration in 20 patients hospitalized with acute decompensated congestive heart failure with fluid overload and either known renal insufficiency (serum creatinine ≥ 1.5 mg/dl) or diuretic resistance. Patients were ineligible for participation if they had hematocrit $\geq 40\%$, renal disease requiring dialysis, systolic blood pressure < 85 mm Hg, known hypercoagulability, had received more than one IV dose of diuretics or if they required IV inotropes. The investigators followed patients for 90 days after the initiation of treatment. Ultrafiltration was continued until euvolemia was achieved. The patients had an average age of 74.5 years and an average ejection fraction of 31% (range 1% to 65%). The average volume removed with ultrafiltration was 8.6 liters. The median B-type natriuretic peptide (BNP) level decreased from 1,230 to 788 pg/ml and remained stable at 30 days (815 pg/ml). Treatment with ultrafiltration reduced the patients' weight, improved their MLHFQ scores, and improved their Global Assessment of Heart Failure at 30 and 90 days ($p < 0.01$ for all three). There were no significant changes in blood pressure, electrolytes, renal function or hemoglobin. Other adverse events were not reported. Only three patients were rehospitalized after discharge (two for unrelated reasons), compared to ten hospitalizations in the three months prior to ultrafiltration. This study strengthened the safety record of peripheral ultrafiltration and presented evidence for clinical efficacy that lasted at least three months

following the hospitalization. However, without matched controls, it is unclear whether these patients would have done equally well or better with traditional IV diuretic therapy.

Finally, a third case series reported the experience of continuous ultrafiltration with a newer generation system from CHF Solutions, the Aquadex FlexFlow, in nine patients hospitalized with HF. All patients failed either outpatient or inpatient medical treatment for worsening volume overload. Inclusion and exclusion criteria for this trial were not described. Most patients (6/9) had renal insufficiency at baseline, though 33% did not. The average time of ultrafiltration in this study was 33 hours with 7.0 liters of fluid removed and an average weight loss of 6.2 kg. The only catheter related adverse event was infiltration of the IV in one patient. No other adverse events occurred during ultrafiltration. Once again, peripheral ultrafiltration appeared to be a safe approach to fluid removal in volume overloaded patients and may be particularly useful in patients with congestive HF who fail medical therapy.

Randomized Clinical Trials (RCT)

The first RCT evaluating peripheral ultrafiltration for the treatment of HF, the Relief for Acutely Fluid-Overloaded Patients with Decompensated Congested Heart Failure (RAPID-CHF) trial, was published in 2005.³² The investigators randomized 40 patients admitted with a primary diagnosis of CHF to one eight-hour session of ultrafiltration or usual care. Additional inclusion criteria included the presence of significant lower extremity edema (2+) and at least one other sign of volume overload. Exclusion criteria included severe valvular stenosis, acute coronary syndromes, systolic blood pressure less than 90 mm Hg, hematocrit > 40%, lack of IV access and the use of iodinated radiocontrast within 72 hours. Patients randomized to ultrafiltration were treated with fluid removal rates up to 500 ml per hour for eight hours through a 16 gauge IV catheter placed in the antecubital fossa. Diuretics were held during ultrafiltration, but could be used after ultrafiltration at the discretion of the treating physician. Patients randomized to the usual care group received standard CHF therapies “according to the best medical/community standards,” although this was not further defined in the paper. The primary outcome of the study was weight loss after 24 hours. Secondary endpoints included total volume removal, global CHF and dyspnea assessments, serum electrolytes and length of hospital stay. The published report did not provide any details about randomization or allocation concealment, although presumably some form of blocked randomization was performed in order to guarantee exactly 20 patients in each treatment group. The report did not mention any blinding nor were details of follow-up described, although it appears that follow-up for most outcomes was 100%. The investigators indicated that they used intention to treat analyses.

Twenty patients were randomized to each group at six hospitals in Minnesota. The two groups were well matched with a median age of about 68 years, 70% men, and 74% with an EF<40%. The median volume of

fluid removed was 3.2 liters. Two patients randomized to ultrafiltration were not treated as randomized: in one patient, a peripheral IV could not be placed and in the second, blood could not be withdrawn from the IV catheter. Four patients in the ultrafiltration group had one additional treatment with ultrafiltration. The median dose of IV furosemide used in the first 24 hours was 80 mg for the ultrafiltration group and 160 mg for the usual care group ($p=0.24$). The primary outcome, weight loss at 24 hours, did not differ between groups (2.5 kg versus 1.9 kg, $p=0.24$). Weight loss was also similar in the two groups at 48 hours and 30 days after enrollment. Recorded fluid removal was greater in the ultrafiltration group (4.6 versus 2.8 liters, $p=0.001$). There was a significant decrease in hemoglobin in the ultrafiltration group compared to usual care, but other hemodynamic and laboratory measurements (heart rate, blood pressure, electrolytes, and creatinine) were similar in the two groups. Some of the more patient oriented outcomes favored the ultrafiltration group. Global CHF and dyspnea scores improved more in the ultrafiltration group at 48 hours ($p<0.05$). For example, 31% of patients in the ultrafiltration group reported marked improvement in dyspnea at 48 hours compared to 12% of patients in the usual care group ($p=0.039$). However, this did not translate into earlier discharge from the hospital: the median length of stay was six days for patients in the ultrafiltration group compared to five days in the usual care group (p NS). Additionally, there was one death in the ultrafiltration group and one catheter site infection that required four weeks of antibiotic therapy.

This small trial³² demonstrated that volume could be removed with peripheral ultrafiltration as effectively as with IV diuretics in patients admitted to the hospital with acute decompensated congestive HF, although both groups were treated with large doses of IV furosemide. There were no significant differences in weight loss at any time point. Symptomatic improvement was greater at 48 hours in the ultrafiltration group, but this did not translate into earlier hospital discharge. The treatment was reasonably well tolerated, although treatment could not be initiated in ten percent (2/20) of patients randomized to ultrafiltration, hemoglobin dropped in the ultrafiltration group, and one patient suffered a significant line infection. Thus, this relatively small study suggested that ultrafiltration offers no significant advantages over traditional IV diuretic therapy in this patient population and was associated with small, but real harms.

The UNLOAD trial was the largest randomized trial of ultrafiltration.³¹ The study enrolled 200 patients from June 2004 to July 2005 at 28 centers across the United States. To be eligible, patients were required to be at least 18 years old and be within 24 hours of hospitalization for HF with clear evidence of volume overload. The study excluded patients with acute coronary syndrome, serum creatinine > 3.0 mg/dl, systolic blood pressure \leq 90 mm Hg, hematocrit >45%, lack of venous access, use of IV pressors, use of vasoactive drugs prior to study entry, use of iodinated contrast, contraindications to transplant, heart transplant, systemic infection, or comorbidities expected to prolong hospitalization. Unfortunately, the investigators do not report

the number of patients with HF who did not meet the entry criteria for the study. This makes it difficult to assess the generalizability of the trial results.

Patients were randomized to receive ultrafiltration or IV diuretics. No blinding was reported. All patients were treated with standard fluid restriction to two liters per day and sodium intake limited to two grams per day. Medications, including angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers were continued in all patients. Patients in the ultrafiltration group were anticoagulated with heparin and treated without IV diuretics for the first 48 hours after randomization. The duration and rate of fluid removal were left to the discretion of the treating physicians. Similarly, those patients randomized to the IV diuretic arm were treated according to the preferences of the treating physician, although the minimum dose of diuretics was required to be at least twice that of the pre-hospitalization oral dose for the patient.

The primary endpoints of the trial were weight loss and the patients' score on a 7-point Likert scale for dyspnea assessed 48 hours after randomization. The primary safety endpoints were changes in serum blood urea nitrogen levels, creatinine, and electrolyte levels and episodes of hypotension. Patients requiring IV vasodilators or pressors during the first 48 hours were considered treatment failures. Secondary efficacy endpoints included fluid loss at 48 hours, length of hospital stay, change in BNP levels, changes in NYHA functional class, MLHFQ scores, Global Assessment scores on a 7-point Likert scale, six-minute walk distance and rehospitalization rates. The protocol pre-specified follow-up evaluation at 48 hours, hospital discharge, and days ten, 30, and 90 after randomization.

Baseline characteristics, including laboratory measurements and medication use, were similar between the two groups. The average age of the patients was approximately 62 years and 69% were men. The majority had reduced left ventricular ejection fraction (70% with $EF \leq 40\%$), peripheral edema (80%), and rales (55%). The only statistically significant difference between the two groups among 32 characteristics reported was for serum potassium (4.0 vs. 4.2, $p=0.028$). This difference was unlikely to be of clinical significance with respect to the outcomes of the study. At 48 hours, patients in the ultrafiltration group had greater weight loss (5.0 vs. 3.1 kg, $p=0.001$), but the dyspnea scores were similar in the two groups (6.4 vs. 6.1, $p=0.35$). Interestingly, there was no correlation between weight loss (and fluid loss) and the dyspnea score. Changes in serum creatinine were similar in the two groups at all time points, but generally favored the diuretic group. For example, at 48 hours, the percentage of patients with > 0.3 mg/dl rise in serum creatinine was 26% in the ultrafiltration group versus 20% in the diuretic group ($p=0.43$). Hypokalemia was more common in the diuretic group (1.3% versus 12%, $p=0.018$). Hypotension rates were similar in both groups (4% vs. 3%, p NR). The quality of life and functional assessments were similar in each group at each assessment through 90 days. These included the NYHA functional class, the MLHFQ scores, 6-minute walk distance, Global

Assessment scores and BNP levels. The length of stay did not differ between the two groups without even a trend towards shorter hospitalizations in the ultrafiltration group (6.3 vs. 5.8 days, $p = 0.98$). However, rehospitalization rates were much lower in the ultrafiltration group (18% vs. 32%, $p=0.037$). The number of deaths was similar in the two groups (9 versus 11, p NR).

The number of adverse events associated with ultrafiltration was low. Two patients had a total of five filters clot, but the filters were replaced and ultrafiltration completed successfully in all cases. Three patients complained of discomfort at the IV site and one patient had a central venous catheter infection. Fewer patients in the ultrafiltration group had bleeding events than those in the diuretic group (1 vs. 7, p NR).

The UNLOAD trial appears to have been well done, though there are a number of methodologic concerns. It is likely that some form of stratified block randomization was done to guarantee exactly 100 patients in each group of the trial, although this was not reported. No blinding for patients, investigators, staff, or those assessing and adjudicating outcomes was reported. This may be less important for the “hard outcomes” of death and rehospitalization rates, but certainly could have affected unreported co-interventions that may have had an influence. It also would have been more credible to have the sites follow a standard protocol for the settings used for ultrafiltration and dose adjustments for IV diuretics than to leave it to physician discretion. Other methodologic concerns include inadequate reporting of recruitment and follow-up. The primary publication does not present a Figure 1 documenting recruitment, randomization, and drop-out from the study as recommended by the CONSORT group.⁴⁰ Thus, it is difficult to follow the flow of patients in the study. Follow-up was clearly incomplete at different time points: approximately 90% of patients had blood test results at 24 hours and only 70% had results at 48 hours. Furthermore, data for the primary endpoints, weight loss at 48 hours and dyspnea scores at 48 hours, were only available on 80% to 84% of the patients randomized. This remarkably high rate of incomplete data 48 hours after randomization in a hospitalized patient population was never explained by the investigators.

The UNLOAD trial presented provocative results. Because it represents by far the largest and highest quality trial of ultrafiltration, its findings have the greatest weight in the overall assessment of ultrafiltration in this review. Volume was clearly more efficiently removed with ultrafiltration compared with IV diuretic therapy as documented by the more rapid weight loss and fluid loss. Adverse events were minimal. However, initial patient oriented outcomes, such as dyspnea scores and walking distance, did not differ between patients. This likely explains the similar length of stay between the two groups (with a non-statistically significant 0.5 day longer average hospitalization for the ultrafiltration group), even though fluid removal was more efficient with ultrafiltration. On the other hand, important intermediate term outcomes strongly favor the ultrafiltration group. There was a trend towards fewer deaths in the ultrafiltration group and

an impressive reduction in rehospitalizations during 90 days of follow-up (an absolute reduction of 14%, number needed to treat (NNT) = 7 to prevent one rehospitalization). Because this large difference was unexpected and is not explained by intermediate measures of HF severity and was not a primary outcome of the study, the result needs to be replicated before it can be accepted with confidence. Furthermore, the methodologic issues discussed in the prior paragraph raise some questions about the validity of the trial. Finally, the patients studied in the trial do not meet the FDA indication for peripheral ultrafiltration as they had not previously failed diuretic therapy.

TA Criterion 3 is not met.

TA Criterion 4: The technology must be as beneficial as any established alternatives.

The established therapy for the treatment of acute decompensated HF is IV diuretics plus vasodilators and inotropes as needed. Both the RAPID-CHF trial³² and the UNLOAD trial³¹ directly compared these two approaches in randomized trials. As noted under TA criterion 3, the quality of the randomized trials was modest at best due to the complete lack of blinding in the trials, inadequate accounting for patients in the trials, and the limited reporting on the process of randomization and allocation concealment. It is clear from the trials that fluid removal and weight loss are greater with ultrafiltration than with diuretic therapy, although some authors have criticized the trials for inadequate dosing of the diuretic therapy.⁴¹ However, the more rapid removal of fluid did not translate into any apparent short term clinical benefits to the patients. Patient scores on quality of life and functional measures were equivalent between the two groups and in both randomized trials there was a trend towards earlier discharge of patients in the diuretic group, not the ultrafiltration group. If clinical results are equivalent between the two groups, then the risk of infection from the two large bore IV catheters needed for peripheral ultrafiltration and the risks of bleeding and heparin induced thrombocytopenia associated with the anticoagulation needed to prevent filter thrombosis are not worth taking. However, the UNLOAD trial reported a large difference in the rehospitalization rates between the ultrafiltration and diuretic therapy groups. This was a somewhat unexpected finding. As such, it needs to be replicated before advocating a change in the long-established approach to the management of a common clinical problem. It may also be more appropriate to target ultrafiltration to the subgroup of patients most likely to benefit from the new technology. So far, the trials have not identified such a subgroup of patients.

TA Criterion 4 is not met.

TA Criterion 5: The improvement must be attainable outside the investigational setting.

The two randomized trials implemented peripheral ultrafiltration at multiple sites across the country. The protocol appears to be relatively simple to follow and likely to be reproducible outside the investigational setting. However, the benefits of peripheral ultrafiltration remain to be proven, so TA criterion 5 is not met.

TA Criterion 5 is not met.

CONCLUSION

Acute decompensation of CHF leads to more than one million hospital admissions per year in the United States. The recommended initial treatment is IV diuretic therapy with the addition of vasodilators and inotropic medications as needed. Inadequate response to therapy, in part because of renal hypoperfusion due to the underlying HF, is common. Ultrafiltration has been demonstrated to be an effective adjunct to standard therapy in initially unresponsive therapy. Ultrafiltration may have additional benefits related to less activation of neuroendocrine responses than high-dose diuretic therapy. However, traditional ultrafiltration has required central venous access and treatment either in the ICU or a dialysis unit. Recently, a device has been developed that allows ultrafiltration to be performed through two peripheral IV catheters without the need for specialized nursing care. The FDA has approved use of the peripheral ultrafiltration device for patients who have failed diuretic therapy.

Three small case series demonstrated the feasibility of removing large volumes of fluid with the peripheral ultrafiltration device. Up to nine liters of fluid were removed from volume overloaded HF patients through ultrafiltration without significant episodes of hypotension, renal dysfunction, electrolyte abnormalities or change in hemoglobin. In one study, HF symptoms improved and weight loss was maintained for at least 90 days. Adverse events were minimal. Thus, peripheral ultrafiltration appeared to be safe and potentially effective for the treatment of volume overload related to HF. However, none of the studies published to date have addressed the effectiveness of the device among patients who have failed diuretic therapy.

One small (RAPID-CHF) and one intermediate sized (UNLOAD) randomized trial (n = 20 and 100 respectively randomized to ultrafiltration) directly compared ultrafiltration with the peripheral device to standard therapy in patients admitted with HF. There were a number of exclusion criteria which may limit generalizability of the results and neither of the trials was blinded. The primary outcome in both trials was weight loss. The ultrafiltration group lost more weight after 48 hours in the larger trial. However, dyspnea scores and the global response to therapy did not differ between the two groups. In both trials, there was a trend towards longer hospitalization stays in the ultrafiltration group. Thus, clinical outcomes did not seem

better with ultrafiltration. Even though the adverse events were minimal, the added complexity of care, including anticoagulation, and the harms due to possible catheter infection (1/120 patients required a four-week course of antibiotics for catheter infection) suggest that on balance the harms outweigh the benefits. However, there was a relatively surprising finding of a significant reduction in rehospitalizations during the 90 days following the initial treatment with ultrafiltration (18% vs. 32%, $p=0.04$). Prior studies have documented sustained reductions in neuroendocrine activation with ultrafiltration compared with IV diuretic therapy, a possible explanation for this finding. This large and clinically meaningful benefit would be worth the small risks associated with ultrafiltration. However, this finding requires replication in a second large clinical trial because it was a somewhat unexpected secondary outcome. Given the large number of HF hospitalizations in the United States, this is clearly a feasible and important trial to undertake in order to confirm the initial findings of the UNLOAD trial. Until that time, peripheral ultrafiltration, while promising, should remain investigational.

RECOMMENDATION

It is recommended that the use of peripheral ultrafiltration does not meet Technology Assessment Criterion 3, 4 and 5 for safety, effectiveness and improvement in health outcomes when used to treat acute decompensated heart failure.

The California Technology Assessment Forum voted to accept the recommendation as written.

June 20, 2007



RECOMMENDATIONS OF OTHERS

Blue Shield Blue Cross Association (BCBSA)

The BCBSA Technology Evaluation Center has not conducted an assessment of this technology.

Centers for Medicare and Medicaid Services (CMS)

CMS is silent regarding the use of Ultrafiltration for the treatment of acute decompensated heart failure.

California Chapter of the American College of Cardiology (CAACC)

A CA ACC representative participated in the discussion at the meeting. The ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines was published in the JACC and is available on the World Wide Web at: <http://content.onlinejacc.org>.

Heart Failure Society of America (HFSA)

The HFSA does not have a formal position regarding the use of this technology. A representative did not attend the meeting. The HFSA Guideline: Evaluation and management of patients with acute decompensated heart failure: HFSA 2006 comprehensive heart failure practice guideline is available at www.guideline.gov.

ABBREVIATIONS

CHF: Congestive heart failure

BNP: B-type natriuretic peptide

HF: Heart Failure

ACE: Angiotensin converting enzyme

ICD's: Implanted cardioverter defibrillators

IV: Intravenous

FDA: Food and Drug Administration

DARE: Database of Abstracts and Reviews

UNLOAD: Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure

NYHA: New York Heart Association

MLHFQ: Minnesota Living with Heart Failure Questionnaire

SAFE: Simple Access Fluid Extraction

RAPID-CHF: Relief for Acutely Fluid-Overloaded Patients with Decompensated Congested Heart Failure

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